AF
1600

DOCKET NO.: ISIS-2710

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Krotz et al.

Application No.: 09/032,972

Filing Date: February 26, 1998

Confirmation No.: 1518

Group Art Unit: 1623

Examiner: Lawrence E. Crane

For: Methods For Synthesis of Oligonucleotides

DATE OF DEPOSIT: April 28, 2003

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID, ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, DC 20231.

John A Harrelson, Jr

TYPED NAME: John A. Harrelson, Jr.
REGISTRATION NO.: 42,637

Box ☒ NON-FEE
☐ AF

Assistant Commissioner for Patents
Washington DC 20231

Sir:

REPLY TRANSMITTAL LETTER

Transmitted herewith for filing in the above-identified patent application is:

☐ A Preliminary Amendment.

☒ An Amendment Responsive to the Office Action Dated February 4, 2003.

☐ An Amendment Supplemental to the Paper filed

☐ Other:

☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27.

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

- ☐ an Independent Inventor
- ☐ a Small Business Concern
- ☐ a Nonprofit Organization

☐ This application is no longer entitled to small entity status. It is requested that this be noted in the files of the U.S. Patent and Trademark Office.

☐ Loss of Entitlement Enclosed

☐ Substitute Pages of the Specification are enclosed.

☐ An Abstract is enclosed.

☐ Sheets of Proposed Corrected Drawings are enclosed.

☐ A Certified Copy of each of the following applications: is enclosed.

☐ An Associate Power of Attorney is enclosed.

☐ Information Disclosure Statement.

- ☐ Attached Form 1449.
- ☐ A copy of each reference as listed on the attached Form PTO-1449 is enclosed herewith.

☐ Appended Material as follows:

☐ Other Material as follows:

FEE CALCULATION

☒ No Additional Fee is Due.

				SMALL ENTITY		NOT SMALL ENTITY	
	REMAINING AFTER AMENDMENT	HIGHEST PAID FOR	EXTRA	RATE	FEE	RATE	FEE
TOTAL CLAIMS	42	42 (20 MINIMUM)		$9 EACH	$	$18 EACH	$0
INDEP. CLAIMS	3	3 (3 MINIMUM)		$42 EACH	$	$84 EACH	$0
FIRST PRESENTATION OF MULTIPLE DEPENDENT				$140	$	$280	$0
☐ ONE MONTH EXTENSION OF TIME				$55	$	$110	$0
☐ TWO MONTH EXTENSION OF TIME				$205	$	$410	$0
☐ THREE MONTH EXTENSION OF TIME				$465	$	$930	$0
☐ FOUR MONTH EXTENSION OF TIME				$725	$	$1450	$0
☐ FIVE MONTH EXTENSION OF TIME				$985	$	$1970	$0
☐ LESS ANY EXTENSION FEE ALREADY PAID				minus	($)	minus	($0)
☐ TERMINAL DISCLAIMER				$55	$	$110	$0
☐ OTHER FEE OR SURCHARGE AS FOLLOWS:							
TOTAL FEE DUE					$		$0

☐ A check in the amount of **$ .00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account 23-3050.

☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of to and through comprising an extension of the shortened statutory period of month(s).

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 23-3050. This sheet is provided in duplicate.

☐ The foregoing amount due for filing this paper.

☒ Any additional filing fees required, including fees for the presentation of extra claims under 37 CFR § 1.16.

☒ Any additional patent application processing fees under 37 CFR § 1.17 or 1.20(d).

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the U.S. Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: April 28, 2003

John A. Harrelson, Jr.
Registration No. 42,637

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

#31
5-12-03
Leonie
NE

ISIS-2710

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1623

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Achim H. Krotz et al.

Serial No.: 09/032,972 **Group Art Unit: 1623**

Filed: February 26, 1998 **Examiner: L. E. Crane**

For: Methods for Synthesis of Oligonucleotides

D. N

I, **John A. Harrelson, Jr.**, Registration No. **42,637** certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On April 28, 2003

John A Harrelson, Jr

John A. Harrelson, Jr., Reg. No. **42,637**

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE

This is in response to the Final Rejection mailed February 4, 2003.

Claims 1-42 are pending in the present application.

Claims 1-42 are rejected under 35 U.S.C.§103(a) for alleged obviousness over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar", PTO-892 ref. A) in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers", PTO-892 ref. G) and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler", PTO ref. H) and further in view of Sproat et al. (PTO-892 Ref. W), Conway, et al. (PTO-892 Ref. Y), Atkinson et al. (PTO-892 Ref. Z), and Sproat et al. (PTO-892 Ref. RA). Applicants respectfully request reconsideration and withdrawal of the rejection.

As admitted in the Office Action, at least two parts of the instant claims are not disclosed by Ravikumar or the other six cited references (page 2 of the February 4, 2003 Final Rejection). The Final Rejection quite correctly states that the art does not show "i) the choice of solvent or solvent mixture present for deprotection strep (c) and ii) the choice of substrate as a linear oligonucleotide as opposed to the branched oligonucleotide of the prior art" (*Id.*). In an attempt to fill the gaps in the art, the Office alleges that Caruthers and Froehler "motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation." However, this is not a fair characterization of the cited references. The Final Rejection cites four solvents– each outside the scope of the instant claims-- disclosed in the Caruthers reference as a basis for the alleged motivation. These solvents, as admitted in the Office Action (page 4 of the February 4, 2003 Final Rejection), were in the context of the coupling step **not the deprotection step**. The Office Action, however, alleges that "the same teaching *appears* to also apply to the deprotection step" (*Id.*, emphasis added). Applicants see no basis for this statement as the Caruthers reference explicitly states that only the solvent teaching is in the context of the coupling reaction (column 5, lines 10-14 of the Caruthers reference).

The Froehler reference also does not motivate the selection of the solvents used in the instant invention for the deprotection step. Froehler, which does not disclose

the instant deprotection solvents, merely states that other deprotection procedures are known to one skilled in the art. It does not follow that the instantly used solvents would selected by one skilled in the art. Applicants respectfully submit that nothing in the remaining cited art shows or motivates Applicant's use of the solvent of the instant claims.

In the absence of any motivation to select the instant deprotection solvents, the instant rejection amounts to an "obvious to try" rejection. *Without the legally required teaching of motivation to make the combination or modification,* the rejection is improper. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1998). The cited art does not provide the teaching or motivation asserted by the Office Action. Applicants request reconsideration and withdrawal of the rejection.

Claims 1-42 are rejected under 35 U.S.C.§103(a) for alleged obviousness over Horn et al., *Nucleic Acids Research* **1989**, *17*, 6959-6967 ("Horn WA"), in view of Horn et al., *Nucleosides and Nucleotides*, **25**, 4842-4849 (1997) ("Horn UA"). Applicants traverse the rejection because the cited art does not fairly suggest Applicant's invention.

Even if one combined selected teaching of the cited art, one would not arrive at any claimed invention. The cited art, for example, does not disclose the use of the deprotection solvent of the instant claims with linear oligomers. The Office Action alleges that the Horn UA reference shows such a use. Horn UA, however, discloses use of toluene/CH_2Cl_2 deprotection solvent, not the solvent of the instant claims. The language "the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent"of instant claims 1 and 21 preclude use of CH_2Cl_2 solvent. Because the cited art cannot produce any claimed invention, Applicants respectfully submit that the rejection should be withdrawn.

Further, Applicants assert that one skilled in the art would not look to the branched oligonucleotide art for deprotection schemes for linear oligonucleotides. The Horn WA reference describes the synthesis of branched oligodeoxyribonucleotides. This reference states that the standard deprotecting reagent was found to be ineffective for deprotection of the synthesized branched DNA, and that trityl deprotection of such branched structures was achieved using 3% dichloroacetic acid in toluene. Applicants note that in the context of the present invention, i.e., synthesis of linear oligonucleotides, the occurrence of branched structures such as described in the Horn WA reference are contaminants to be avoided, and, in the event that such branch structures are produced, it is highly desirable to avoid deprotecting them, both to eliminate participation in further synthesis cycles, and in order to utilize the trityl groups to eliminate the contaminant from the final purified linear oligonucleotide. Further, the Horn WA reference states at page 6965:

> In our early attempts to synthesize **branched DNA**, we found it difficult to deprotect the multiple intramolecular dimethoxytrityl functions with **standard DCA/CH_2Cl_2** even with extended exposure (2). Under the assumption that dimethoxytrityl stacking stabilize the protection, we employed 3% (v/v) DCA in toluene. With this solution it was possible to rapidly and efficiently detritylate the branched materials (Figure 2). (emphasis added)

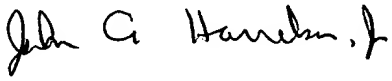
Thus, the Horn WA reference teaches 1) that **deprotection with dichloroacetic acid in methylene chloride is *standard***; and that 2) the toluene solution was needed for deprotection of **branched DNA**, which posed particular problems. As such, Applicants assert that those of skill in the art would not be led to use the stringent deprotection regime disclosed in the Horn WA reference for standard synthesis of linear oligonucleotides.

The Office Action has not set forth how any reference would have instructed the person of ordinary skill in the art to modify the reference teachings to afford the claimed invention. No reference teaches or fairly suggests deprotecting the 5'-hydroxyl group of a linear oligonucleotide, with a protic acid, in a solvent system consisting essentially of an aromatic, alkyl aromatic, halogenated aromatic, halogenated alkyl aromatic, or aromatic ether solvent. Nor does any reference teach or fairly suggest to the person of ordinary skill in the art how to choose suitable deprotecting solvents from the myriad of possibilities. Absent these motivating factors, the Office Action has failed to establish that the person having ordinary skill in the art would have been motivated to substitute the instant solvent for the solvent of the prior art. For at least these reasons, Applicants request reconsideration and withdrawal of the rejection.

Applicants submit that the claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment.

Respectfully Submitted,



Date: April 28, 2003

John A. Harrelson, Jr.
Registration No: 42,637

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Tel: (215) 568-3100
Fax: (215) 568-3439